PATENT COOPERATION TREATY

PCT

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INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference ABL-005-PCT3	**FOR FURTHER ACTION** See Form PCT/IPEA/416	
International application No. PCT/BE2004/000002	International filing date *(day/month/year)* 09.01.2004	Priority date *(day/month/year)* 10.01.2003
International Patent Classification (IPC) or national classification and IPC C07K16/36, C07K16/18, C12N15/13, A61K39/395, A61K38/49, A61P7/02, A61M31/00		
Applicant ABLYNX N.V.		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 9 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☐ *sent to the applicant and to the International Bureau)* a total of sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☒	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
09.08.2004	22.12.2004
Name and mailing address of the international preliminary examining authority: European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Authorized Officer Le Flao, K Telephone No. +31 70 340-1040

Form PCT/IPEA/409 (Cover Sheet) (January 2004)

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/BE2004/000002

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

   Description, Pages

   1-97 as originally filed

   Claims, Numbers

   1-32 as originally filed

   Drawings, Sheets

   1/19-19/19 as originally filed

   ☒ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 29

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (specify):

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the said claims Nos. 29

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-28,30-32
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-28,30-32
Industrial applicability (IA)	Yes:	Claims	1-28,30-32
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Supplemental Box relating to Sequence Listing

Continuation of Box I, item 2:

1. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this report has been established on the basis of:

   a. type of material:

   ☒ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☒ in written format

   ☒ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed

   ☐ filed together with the international application in computer readable form

   ☒ furnished subsequently to this Authority for the purposes of search and/or examination

   ☒ received by this Authority as an amendment on

2. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional observations, if necessary:

Re Item III.

Present claim 29 relates to a compound defined by reference to a desirable characteristic or property, namely "that modulates platelet-mediated aggregation identified according to the method of claim 27". The claims cover any compound having this characteristic or property, whereas the application provides no support within the meaning of Article 6 PCT and no disclosure within the meaning of Article 5 PCT for such compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claim also lacks clarity (Article 6 PCT). An attempt is made to define the compound by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, no the search has been carried out for this claim and no opinion with regard to novelty, inventive step and industrial applicability will be established.

Re Item V.

1 The following documents are referred to in this communication:

D2 ARBABI GHAHROUDI M ET AL: "Selection and identification of single domain antibodies fragments from camel heavy-chain antibodies" FEBS LETTERS, vol. 414, no. 3, 15 September 1997, pages 521-526, XP002069903

D3 US 2002/028204 A1 (KITO MORIKAZU ET AL) 7 March 2002

D4 MUYLDERMANS S: "Single domain camel antibodies: current status" REVIEWS IN MOLECULAR BIOTECHNOLOGY, vol. 74, no. 4, June 2001, pages 277-302, XP001057480

D5 US 6 251 393 B1 (MCLEOD ANNE ET AL) 26 June 2001

2 **NOVELTY**

2.1 Claims 1-28 and 30-32 are novel since none of the cited document discloses single domain antibody against vWF, vWF A1 domain, A1 domain of activated vWF, vWF A3 domain, gpib or collagen.

3 **INVENTIVE STEP**

3.1 The present application does not meet the criteria of Article 33(1) PCT, because the subject matter of claim 1 does not involve an inventive step in the sense of Article 33(3)PCT.

Document D3, which is considered to represent the most relevant state of the art to the subject matter of claim 1, discloses (the references in parenthesis applying to this document) monoclonal antibodies binding to human vWF produced by hybridomas AjvW-1, -2, -3 & -4. These antibodies have anti-thrombotic activity and prevent thrombus formation in vivo (§ 156 - §167). The interest of humanizing them for their use as therapeutic agent and the way to do it is disclosed (§70 - §71).

The subject-matter of claim 1 differs from the disclosure of D3 in that the antibody has a different structure which is a single domain antibody. The effects of the difference appears to be those of VHHs antibodies.

The problem to be solved by the present invention may therefore be regarded as the provision of improved anti vWF or anti collagen antibodies.

In view of **D2** the solution proposed in claim 1 of the present application cannot be considered as involving an inventive step (Article 33(3) PCT) for the following reasons: Document **D2** discloses the immunisation of dromedary with tetanus toxoid and lysozyme, the isolation of mRNA from the blood, the construction of a library and the selection of soluble VHH fragments. The interest of such VHHs for preparing multivalent binders **having an increased avidity is mentioned** (p.521, right-hand column, §4,5 ; p.522, left-hand column ; p.525, right-hand column, §3). It is therefore considered that the skilled person when trying to solve the problem posed would apply the teaching of D2 for obtaining a VHH antibody anti vWF. The preparation of VHHs antibodies itself is not considered inventive : it is a known technique as confirmed in documents published before the filing date and describing such a method (see also D4 and D6). Applying a known technique for preparing antibodies to another particular protein, here vWF or collagen is not considered to require inventive skills.

3.2 Providing bivalent, multivalent or humanised antibodies is also not considered to involve an inventive step since document D2 discloses advantages of bivalent and multivalent forms and D3 disclosed the interest of humanised antibodies. The

antibodies corresponding to the sequences of claims 4 & 5 have not been shown as having a particular effect. The subject-matter of claims 2-6 is therefore not considered as involving an inventive step.

3.3 Claims 14, 15 and 22 relating to composition and claims 16-21 and 30-32 relating to the therapeutic use and the diagnostic use of the antibodies are anticipated by D3 which discloses the therapeutic and detection uses of anti vWF antibodies. Such claims are therefore not considered to involve an inventive step. For the same reasons the subject-matter of claims 25 and 26 relating to a method for treating invasive medical devices and of claims 23 and 24 relating to the method of producing the antibody are also considered not to involve an inventive step.

3.4 Part of the dependent claims 7-13 could meet the requirements of Article 33(3) PCT. As a matter of fact some of the prepared antibodies have a particular effect that could support the inventive step of a claim related specifically to them. This appears to be the case for the antibodies corresponding to SEQ ID NO: 8, 9 and 11 that were shown to inhibit completely platelet aggregation at high shear and for the antibodies corresponding to SEQ ID NO: 3, 5, 7, 10 and 12 that have also strong inhibition capacity. However the antibodies corresponding to SEQ ID NO: 23 - 29 and 31 do not inhibit platelet aggregation or do in a lesser extent and at much higher concentration than the ones cited just above. As a consequence not all the antibodies of the present application present a particular effect.

3.5 Without limiting the claims either with the essential technical feature responsible for the particular effect or to the particular antibodies that were shown to have the effect no inventive step can be acknowledged for the subject-matter of claims 1-26 & 30-32.

4 INVENTIVE STEP AND SUPPORT

4.1 Claims 27 and 28 relating to a method of identifying an agent that modulates platelet-mediated aggregation comprising contacting a polypeptide construct according to claims 1 to 12 and to a kit for screening for agents that modulate platelet-mediated aggregation are speculative, not supported as required by Article 6 PCT and not disclosed in the description as required by Article 5 PCT. These claims are attempting to solve a hypothetical problem without providing a solution. As a consequence it is not considered that such claims involve inventive step.

5 INDUSTRIAL APPLICABILITY

5.1 For the assessment of the present claims 16-21 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re item VIII.

Claims 1-12 are not supported by the description as required by Article 6 PCT, as their scope is broader than justified by the description and drawings. The reasons therefor are the following: the examples deal with Camelidae VHHs antibody against vWF A3, vWF A1, against collagen, against mouse serum albumin, and bispecific combinations thereof. The description and examples convey the impression that the polypeptides claimed can only be prepared as camelidae VHHs and no alternative forms are envisaged. Claim 1 is therefore missing this essential technical feature thereby not fulfilling the requirements of Rule 6.3 PCT. The term "a polypeptide construct comprising at least one single domain antibody directed against ..." is too vague and inappropriate and the claims 1-12 are not supported by the description as required by Article 6 PCT.

Claims 3, 11 and 12 do not meet the requirements of Article 6 PCT in that the matter for which protection is sought is not clearly defined. The following functional statements do not enable the skilled person to determine which technical features are necessary to perform the stated function: fragment thereof, homologous sequence, a functional portion.